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Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 06/06/2003 in respect of Patent Application No. 586/MUM/2003 of CADILA HEALTHCARE LIMITED, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India.

This certificate is issued under the powers vested in me under section 147(1) of the Patents Act,1970.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Dated this 25th day of June 2004.

(R.BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS.

BEST AVAILABLE COPY

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

1. We, M/s Cadila Healthcare Limited, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

2. Hereby declare-

   a) That we are in possession of an invention titled
   "ANTIINFECTIVE COMPOUNDS, PROCESS FOR THEIR PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

   b) That the **provisional specification** relating to this invention is filed with this application.

   c) That there is no lawful ground of objection to grant of a patent to us.

3. Further declare that the true and first inventors for the said invention are:
   1) BAROT, Vijay Kumar Gajubhai &
   2) KOTHARI, Himanshu Madhusudanbhai
   (both Indian Citizens of Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India)

4. We, claim the priority from the application filed in convention countries, particulars of which are as follows: NIL

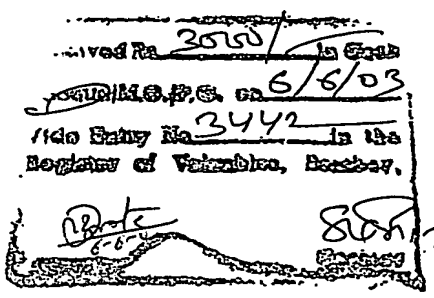
5. That we are the assignee or legal representatives of the true and first inventors.

6. That our address for service in India is as follows:

   M/s Subramaniam, Natraj & Associates
   Attorneys-At-Law
   E-556, Greater Kailash-II
   New Delhi - 110 048, India.

   Phone: +91 11 29215603, 29226012, 29216025
   Facsimile: +91 11 29226005
   Email: sna@vsnl.com

586/mum/2003
6/6/2003



(7) Following declaration was given by the inventors

We, **Vijay Kumar Gajubhai BAROT and Himanshu Madhusudanbhai KOTHARI,** both Indian citizens, of CADILA HEALTHCARE LIMITED, Zydus Towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India,

and the true and first inventors for this invention declare that the applicants herein is our assignees.

VGB

Vijay Kumar Gajubhai BAROT

Himanshu Madhusudanbhai KOTHARI

(8) That to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to us on this application.

(9) Following are the attachments with this application:
- (a) Provisional specification in triplicate
- (b) Statement and Undertaking on FORM 3 in duplicate
- (c) Power of Authority
- (d) Form 2 in triplicate
- (e) Power of Authority
- (f) Abstract

Fee Rs. ..... in Cash/Cheque/Bank Draft Bearing No..... dated.....on .....Bank.

We request that a patent be granted to us on any complete specification filed on this application for the said invention.

Dated this 5th day of June , 2003.

(Dr. Braj Bhushan Lohray, President, Zydus Research Centre)
for CADILA HEALTHCARE LIMITED

To
The Controller of Patents
The Patent Office, at Mumbai

FORM 2

The PATENT ACT, 1970
(39 of 1970)
Provisional Specification

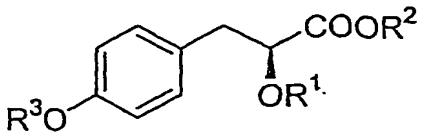
An improved process for the preparation of S (-) 3-aryl-2-hydroxy propanoic acid derivatives without any resolution.

CADILA HEALTH CARE LTD, Zydus Research Centre
Zydus Tower, Satellite Cross Road, Sarkhej-Gandhinagar Highway,
Ahmedabad-380015, Gujarat, India

The following specification describes the nature of the invention and the manner in which it is to be performed:

Field of invention

The present invention relates to a process for the preparation of S (-) 3-aryl-2-hydroxy propanoic acid derivatives of the structural formula (1),



(1)

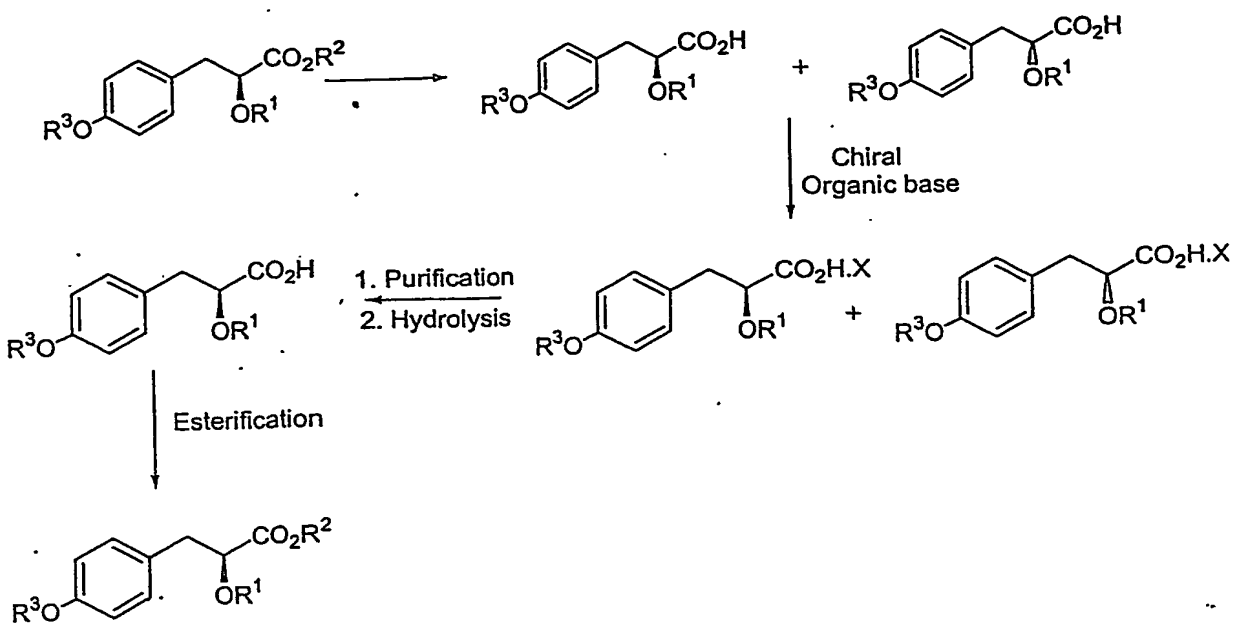
The compound of formula (1) where R^3 = -H, is useful as an intermediate for the preparation of many pharmaceutically active compounds.

Background of invention

S(-) 3-aryl-2-hydroxy propanoic acid derivatives are essential intermediates for the preparation of a number of promising drugs. These compounds also have been considered useful for the treatment of eating disorders. They are also used as sweetening agents, in photosensitive materials and also in liquid crystals.

Background & prior art

Preparation of S (-) 3-aryl-2-hydroxy propanoic acid derivatives are reported by several methods in the literature such as by classical resolution i.e. by crystallization of diastereomeric salts of the racemates, by using chiral precursor etc. but in all the processes at one stage resolution of an intermediate has to be carried out to obtain optically pure S (-) isomer of structural formula (1) (where R^3 = H). Such processes are described in WO 0026200, WO 0140159, WO 0224625, WO 9962871 and WO 0063189. Also, the processes described in WO 0026200 (Rao et. al.) uses benzyl bromide for benzylation, which are lachrymatory. Also the assay of benzylated product is less against the reference standard by HPLC in both these processes. Again, in both the processes the debenzylation of the final intermediate was done by using Pd/C under pressure. Such a process is costly and not very efficient at a large scale. WO 0224625 describes a process for preparing chirally pure S (-) alkyl-2-alkoxy-3-(4-benzyloxyphenyl) propanoate. However, the process for obtaining the chirally pure product involves the following steps:



Thus, the process of obtaining the chirally pure product from the partially racemized (S) isomer involves 5 extra steps thereby increasing the manufacturing cost and reducing the overall yield.

Deussen et al. (Organic Process Research & Development, 7, 82-88 (2003)) describes the enantioselective enzymatic hydrolysis of Ethyl-2-ethoxy-3-(4-hydroxyphenyl)propanoate for the large scale production of S (-) isomer of structural formula (1) where R^3=H.

WO 0140159 (Andersson et. al.) describes a process for preparing compounds of formula (I), when R^3 = H, using alkylthiol and base at higher temperature as the deprotecting agent. Also the pure (S) isomer was obtained by a sequence of steps similar to those used in WO 0224625 thereby affecting the manufacturing cost & yield.

Objectives of present invention

The main objective of the present invention is to provide an improved process for the preparation of S (-) 3-aryl-2-hydroxy propanoic acid derivatives of formula (1) with high chemical and chiral purity.

A preferred objective is to prepare a compound of formula (1), when R^3=H, having more than or equal to 99.5% e.e. by HPLC analysis without any resolution.

Another objective of the present invention is to do deprotection of compound of formula (1) to obtain further compound of formula (1), where $R^3 = H$, by using a combination of hard acid and soft nucleophile.

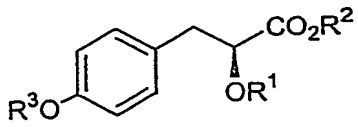
Alternatively, deprotection can be carried out by catalytic transfer hydrogenation reaction with Pd/C and a hydrogen donor at atm. pressure to obtain compound of formula (1), where $R^3 = H$.

Another objective of is to provide a cost-effective, safe and efficient process for obtaining chirally pure compound of formula (1).

A further objective of the present invention is to provide a process for the large scale production of compound of formula (1) in a chirally pure form.

Detailed description of the invention

Accordingly, the present invention describes an improved process for the preparation of the S (-) enantiomer of a compound of the general formula (1).



(1)

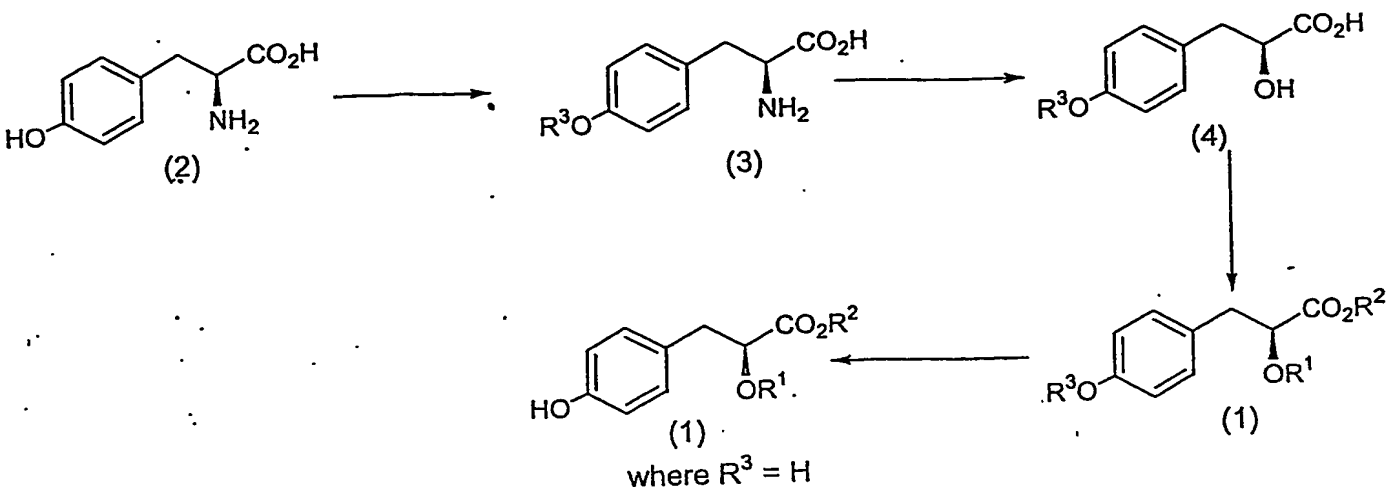
Wherein, R^1 represent H or (C_1-C_6) alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl and the like.

R^2 represents (C_1-C_6) alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl and the like.

R^3 represents H, protecting groups such as benzyl, substituted benzyl, (C_1-C_3) alkyl and like.

Compound of general formula (1) can be prepared according to the following scheme:

Scheme



Step 1: Selective O-alkylation or O-arylation of L- Tyrosine of formula (2) using a base, a chelating agent, an alkyl or aryl halide in the presence of solvents to obtain the compound of formula (3) (according to the general method described in "The practise of peptide synthesis", Bodanszky et. al., pp 50)

The selective O-alkylation or O-arylation of compound of formula (2) can be carried out by reacting a base such as NaOH, KOH, K_2CO_3 and the like, a chelating agent such as $CuSO_4$, Cu $(OAc)_2$ and the like, and an alkyl or aryl halide in the presence of solvents such as aq. methanol, ethanol, DMF and the like or their combination thereof, at 25 °C-65°C. The bases may be present in 2-2.5 equivalents, the chelating agent in 0.5-0.7 equivalents, alkyl or aryl halide in 1-1.5 eq. and the solvent may be present in 5-20 times to the weight of L-tyrosine. In a preferred embodiment, the base used is KOH (2 to 2.2 eq.), the chelating agent is $CuSO_4$ (0.5 to 0.65 eq.), Benzyl chloride is the alkylating agent and the solvent used is aq. DMF at 50°C-60 °C, to afford the copper complex of O-benzyl-L-tyrosine. Thus by substituting aquous methanol (WO 0026200 & WO 0224625) with DMF as the solvent, the rate of reaction is enhanced resulting in higher yield and better purity. Also, the volume of solvent required is reduced substantially (from ~20 times of the starting compound to 4 times the starting compound in case of DMF).

The crude Cu complex obtained above was purified by treating it with methanol at reflux temperature. Cleavage of the Cu complex using dil. HCl yielded the compound (3) in high chemical & chiral purity (e.e.≥ 99%).

Step 2: Diazotisation of the compound of the formula (3) using a diazotising agent, in suitable solvents in acidic media to obtain the compound of formula (4).

Diazotisation of the compound of formula (3) with sodium nitrite in 2-5 equivalents, preferably 3-4 equivalents and strong acids such as sulfuric acid, orthophosphoric acid, conc. HCl in 2-8 equivalents, preferably sulfuric acid in 3-5 equivalents at 0 °C to 25 °C. is carried out in solvents such as dioxane, acetone, methyl isobutyl ketone and the like or their mixtures, preferably in dioxane, to give the compound of formula (4) [Tetrahedron Lett., 25, 2287-2290(1971) & US 5,747,448 which are incorporated herein as reference]. The diazotised product was obtained in high chemical & chiral purity (e.e. ≥ 98%).

Step 3: Dialkylation of the compound of formula (4) using an excess of alkylating agent and excess base, in presence of suitable solvent to obtain optically pure compound of formula (1).

Dialkylation of the compound of formula (4) to get the dialkylated compound of formula (1) with high chemical and chiral purity, was carried out by suitably modifying the process reported by Robert A.W. Johnstone et.al.(Tetrahedron, 35, 2169-2173, (1979)), which describes the alkylation of aliphatic alcohols and acids with alkylating agents at ambient temperature i.e.18°C-20 °C using an excess of potassium hydroxide as a base and DMSO as a solvent.

According to the modified procedure, dialkylation of the compound of formula (4) was carried out using an excess of base to the starting compound, with a suitable alkylating agent in presence of suitable solvent at 0-30 °C to obtain the compound of formula (1). Suitable alkylating agents may be alkyl sulfates such as diethyl sulfate, dimethyl sulfate and the like; alkyl halides selected from methyl iodide, ethyl iodide, ethyl bromide and the like. The solvent used may be DMSO, MIBK, dioxane, and the like or mixtures thereof, preferably DMSO. The base may be present in 2 to 7 equivalents, preferably in 5 to 7 equivalents, the alkylating agent is present in equal moles to the base, and the solvent

may be in the range from 4-10 times the weight of the intermediate of formula (4). By the use of an excess of alkylating agent, the reaction goes to completion and the compound (4) is obtained with high chemical (> 98%) and chiral (ee> 97%) purity. Prior art for this conversion reports the formation of ~20% byproduct and upto 4% racemization. (Deussen et. al. *Organic Process Research & Development*, 2003, 7, 82-88)

The crude product of formula (1) was purified by removal of excess alkyl halide or alkyl sulfate to obtain chemically pure and high chirally pure (ee ≥ 97%) compound of formula (1) without resolution. Removal of excess alkyl halide from the product can be done by vacuum distillation. If alkyl sulfate is used, the excess alkyl sulfate, in presence of an ester group may be removed by treating with an organic base such as triethylamine (1-2 equivalents to alkyl sulfate) in alcohol at reflux temperature of the solvent.

Step 4: Deprotection of the protecting group of compound of formula (1) to obtain further compound of formula (1).

The protecting group can be removed using a hard acid and soft nucleophile, optionally in the presence of a solvent at 0 °C-40 °C to obtain the chirally pure (ee ≥ 99.5 %) compound of formula (1), (where R^3= H). The deprotection has to be carried out in the presence of an ester group. Suitable acids for carrying out such deprotection may be Lewis acids such as $AlCl_3$, BF_3 ethereate, BF_3 acetate and the like, preferably BF_3 ethereate in 1.5 to 6 equivalents. Suitable nucleophiles may be alkylthiols like ethanethiol, propanethiol and the like, arylthiols such as thioanisole, thiophenol and the like, preferably thioanisole in 2.5-7 equivalents. Solvents, if required may be selected from DCM, $CHCl_3$ and like or mixtures thereof. The product contains less than or equal to 0.3% of the rearranged product S (-) alkyl-2-alkoxy-3-(3-benzyl-4-hydroxyphenyl) propanoate.

Alternatively, the deprotection can be carried out by catalytic transfer hydrogenation in a suitable solvent using metal catalysts such as Pd/C (5-10%) in the presence of a hydrogen donor reagent, at atmospheric pressure and at a temperature ranging from 25 °C to the reflux temperature of the solvent used, to obtain the compound of formula (1), (where R^3 = H). Suitable solvents which may be used includes ethyl acetate, THF, aq. acetic acid, dioxane, aqueous or non aqueous alcohols such as methanol, ethanol, isopropanol and the

like or their mixtures. Preferably, ethyl acetate in 5-10 volumes is used. Suitable hydrogen donor reagent may be ammonium formate, cyclohexene and the like, preferably ammonium formate in 3-6 equivalent. The compound of formula (1), where R^3= H, is obtained in high optical purity (having 100% e.e) after suitable work up, and chemical purity of more than or equal to 98% by HPLC analysis. The product contains less than or equal to 0.3% of the rearranged product S (-) alkyl-2-alkoxy-3-(3-benzyl-4-hydroxyphenyl) propanoate.

Advantages of the present process:

1. The present invention provides a novel process for the preparation of chemically & chirally pure S (-) 3-aryl-2-hydroxy propanoic acid derivatives of formula (1).
2. The present invention provides a manufacturing process for the preparation of chemically and optically pure compounds of formula (1), without using resolution at any stage.
3. The invention also describes a process of converting compound of formula (2) to compound of formula (3) using DMF as the solvent. This has the benefit of enhancing the reactivity; thereby the reaction goes to completion and the product is obtained in high yield (60%) with high chemical and chiral purity.
4. It provides a novel process for the debenzylation or dealkylation of compound of formula (1) to obtain further compound of formula (1), (where R^3 = H).
5. The present invention provides a very mild and cost effective method for debenzylation of compound of formula (1) to give further compounds of formula (1) unlike Pd/C under high pressure conditions that are normally used in prior art.
6. Another advantage of the process is that it does not involve highly lachrymatory chemicals like benzyl bromide.
7. Another advantage is the reduction of reaction time (2-3 hours) during conversion of compound of formula (3) to (4) compared to that reported in literature (24 - 36 hours, WO 0224625).
8. This invention provides a method to obtain compound of formula (3) in high assay and purity.

9. This invention provides a method to remove excess dialkyl sulfate in the presence of sensitive ester functional group during the conversion of compound of formula (4) to (1) ($R^3 \neq H$).
10. The present invention provides an industrial process for the manufacture of compound of formula (1) which is practical, safe and cost effective.

Dated this 5th **day of** June **2003**

Signature B. B. Lohray
(Dr. B. B. Lohray, President Zydus Research Centre)
for Cadila Healthcare Ltd.

To
The Controller of Patents
The Patent Office,
at_____